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=> s shigella
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L1 1918 SHIGELLA

=> s mammal?

L2 42627 MAMMAL?

=> s l1(p)l2

L3 99 L1(P)L2

=> s entry or entered or enter

152483 ENTRY
89863 ENTERED
219938 ENTER
L4 361399 ENTRY OR ENTERED OR ENTER

=> s l4(p)l3

L5 2 L4(P)L3

=> d 1

1. 5,723,283, Mar. 3, 1998, Method and composition for an early vaccine to protect against both common infectious diseases and chronic immune mediated disorders or their sequelae; John Barthelow Classen, 435/4; 424/184.1, 204.1, 234.1 [IMAGE AVAILABLE]

=> d ab

US PAT NO: 5,723,283 [IMAGE AVAILABLE] L5: 1 of 2

ABSTRACT:
A method of immunization, and compositions therefor, are provided for substantially preventing or reducing the symptoms of at least one infectious disease and at least one chronic immune mediated disorder. An immunogenic challenge which supplements the normal childhood immunization schedule can help ensure the proper maturation of the immune system and prevent the development of chronic immune mediated disorders.

=> d clms

US PAT NO: 5,723,283 [IMAGE AVAILABLE] L5: 1 of 2

CLAIMS:

CLMS(1)

What is claimed is:

1. A method of determining whether an immunization schedule affects the incidence or severity of a chronic immune-mediated disorder in a treatment group of mammals, relative to a control group of mammals, which comprises immunizing mammals in the treatment group of mammals with one or more doses of one or more immunogens, according to said immunization schedule, and comparing the incidence, prevalence, frequency or severity of said chronic immune-mediated disorder or the level of a marker of such a disorder, in the treatment group, with that in the control group.

CLMS(2)

2. The method of claim 1, wherein said chronic immune mediated disorder is diabetes mellitus.

CLMS(3)

3. The method of claim 1 in which the chronic immune mediated disorder is SLE.

CLMS(4)

4. The method of claim 1 in which a first dose of said immunization schedule is given when the mammals are less than 56 days old.

CLMS(5)

5. The method of claim 4 wherein the first dose is given when the mammals are less than 42 days old.

CLMS(6)

6. The method of claim 5 in which the first dose is given when the mammals are less than 14 days old.

CLMS(7)

7. The method of claim 1 wherein said chronic immune mediated disorder is an autoimmune disease.

CLMS(8)

8. The method of claim 1 wherein said immunization schedule prevents at least two infectious diseases.

CLMS(9)

9. The method in claim 1 wherein at least one group receives more than one dose of an immunogen.

CLMS(10)

10. The method of claim 1 wherein the interval between doses is greater than 7 days.

CLMS(11)

11. The method of claim 1 where, within the first 112 days after birth, at least one immunogen is administered in at least four distinct dosings.

CLMS(12)

12. The method of claim 1 wherein, within the first 42 days after birth, at least one immunogen is administered in at least three distinct dosings.

CLMS(13)

13. The method of claim 1, wherein for at least one immunogen, the total dosage during the first 112 days after birth is substantially greater than that required for immunization against the infectious disease with which it is associated.

CLMS(14)

14. The method of claim 1 wherein at least one immunogen is administered by a route other than intravenously.

CLMS(15)

15. The method of claim 1 wherein at least one immunogen is administered subcutaneously, intradermally, or intramuscularly.

CLMS(16)

16. The method of claim 1 wherein the ability of said immunogen or immunization schedule to prevent an infectious disease is also tested.

CLMS(17)

17. The method of claim 1 wherein at least one immunogen is one other than a live vaccine.

CLMS(18)

18. The method of claim 1 wherein at least one immunogen is not a BCG immunogen.

CLMS(19)

19. The method of claim 1 wherein said immunogen is one other than a pertussis immunogen.

CLMS(20)

20. The method of claim 1 wherein at least one of said immunogens is selected from the group consisting of immunogens of diphtheria, tetanus, pertussis, polio, hepatitis A, hepatitis B, hemophilus influenza, measles, mumps, rubella, yellow fever, anthrax, encephalitis, meningococcus, meningitis, pneumococcus, typhus, typhoid fever, streptococcus, neisseria, cholera, cytomegalovirus (CMV), respiratory syncytial virus, influenza, rotavirus, varicella, rabies, yellow fever, Japanese flavivirus, coccidiomycosis, and immunogens that cross react to any of said immunogens.

CLMS(21)

21. The method of claim 1 wherein a dose of immunogen being administered is a pharmaceutically acceptable dose.

CLMS(22)

22. The method of claim 1 wherein incidence of the disorder in the treatment group is compared to the incidence of the disorder in the control group.

CLMS(23)

23. The method of claim 1 wherein the method is part of a production process to test vaccine lots for efficacy or safety.

CLMS(24)

24. The method of claim 1 wherein the method is part of a development process or clinical trial of a vaccine to test a vaccine for safety or efficacy.

CLMS(25)

25. The method of claim 1 wherein at least one group receives an immunogen at a time sufficiently early enough to substantially reduce the incidence or severity of said disorder, sufficient number of mammals are followed after immunization for a sufficiently long interval to ensure that said mammals have an effect lasting for a clinically significant period of time after discontinuation of immunization, and the method does not involve the administration of an live organism leading to the infection of mammals for the duration of the time they are followed.

CLMS(26)

26. The method of claim 1 wherein said mammals are a human.

CLMS(27)

27. The method of claim 1 wherein said mammals are rodents and diabetes has not been chemically induced by streptozotocin.

CLMS(28)

28. The method of claim 1 wherein said mammals are NOD mice or BB rats.

CLMS(29)

29. The method of claim 1 wherein the method is prospective.

CLMS(30)

30. The method of claim 1 wherein said mammals are randomized in said treatment and control groups.

CLMS(31)

31. The method of claim 1 wherein at least one said treatment group receives one potentially pharmaceutically acceptable dose of at least two potentially pharmaceutically acceptable immunogenic agents which comprise at least one potentially pharmaceutically acceptable first pediatric immunogen and at least one agent selected from the group consisting of a second pediatric immunogen and a non-pediatric immunogen.

CLMS(32)

32. The method of claim 1 wherein at least one control group
(i) lacks at least one immunogenic agent/adjuvant that is provided in said immunization schedule;
(ii) includes at least one immunogenic agent/adjuvant that is not provided in said immunization schedule;
(iii) includes a higher dose of at least one immunogenic agent/adjuvant than that provided in said immunization schedule;
(iv) includes a lower dose of at least one immunogenic agent/adjuvant than that provided in said immunization schedule;
(v) includes at least one additional dose of at least one immunogenic agent/adjuvant that is provided in said immunization schedule;
(vi) lacks at least one dose of at least one immunogenic agent/adjuvant that is provided in said immunization schedule;
(vii) includes at least one dose of at least one immunogenic agent/adjuvant at a later time than said immunogenic agent/adjuvant is administered in said immunization schedule;
(viii) includes at least one dose of at least one immunogenic agent/adjuvant at an earlier time than said immunogenic agent/adjuvant is administered in said immunization schedule; or
(ix) has no modifications from said immunization schedule.

CLMS(33)

33. The method of claim 1 wherein at least one group receives an immunogen at a time sufficiently early enough to substantially increase the incidence or severity of said disease.

CLMS(34)

34. The method of claim 33 wherein at least one group receives an immunogen starting after 41 days of life.

CLMS(35)

35. The method of claim 1 wherein the immunogen being studied for its effect on the incidence or severity of said disorder is administered starting after 41 days but before 180 days of life.

CLMS(36)

36. The method of claim 1 wherein said treatment group has not received an autoantigen capable of inducing diabetes.

CLMS(37)

37. The method of claim 1 wherein at least the majority of the mammals in control group did not develop the infectious diseases which are prevented by said immunogen.

CLMS(38)

38. The method of claim 1 wherein mammals are excluded from a treatment group if:
i) said mammals have substantial immunologic protection against the infectious disease which said immunization schedule protects against, or
ii) said mammals have substantial levels of at least one surrogate marker of an autoimmune disease even though the mammals had not been previously diagnosed as having an autoimmune disease, or
iii) said surrogate marker was substantially increased following a previous vaccination, infection or other immunologic challenge.

CLMS(39)

39. The method of claim 1, wherein both a pediatric immunogen and a non-pediatric immunogen are administered.

CLMS(40)

40. The method of claim 1 wherein the mammals are made susceptible to said immune-mediated disorder by administration of an immunosuppressant or by immunosuppressive surgery.

CLMS(41)

41. The method of claim 1 in which the groups are compared for a period from first administration until at least 52 days after the last administration of an immunogen for a rodent and one year for a human.

CLMS(42)

42. The method of claim 1 in which the groups are compared from first administration until at least 24.5 weeks of age in a rodent or 5 years of age in a human.

CLMS(43)

43. The method of claim 1 wherein the level of an autoantibody marker in two groups is compared.

CLMS(44)

44. The method of claim 1 wherein at least one immunogen is administered with a depot adjuvant.

CLMS(45)

45. The method of claim 1 wherein the disorder is not an immune-mediated cancer.

CLMS(46)

46. The method of claim 1, further comprising determining whether the age of the subject mammal, at the time of commencement of the immunization schedule, affects the incidence, prevalence, frequency or severity of the disorder.

CLMS(47)

47. The method of claim 1, wherein the effect of the schedule on the incidence, prevalence, frequency or severity of the disorder is determined at least one year after immunization.

=> s aspartate(4a)dehydrogenase

3269 ASPARTATE
5805 DEHYDROGENASE
L6 115 ASPARTATE(4A)DEHYDROGENASE

=> s l1 and l6

L7 5 L1 AND L6

=> d 1-4

1. 5,716,594, Feb. 10, 1998, Biotin compounds for targetting tumors and sites of infection; David R. Elmaleh, et al., 424/1.41, 1.65, 1.73, 9.36, 114; 514/45, 387; 534/14, 15; 548/302.7, 303.7, 304.1 [IMAGE AVAILABLE]

2. 5,672,345, Sep. 30, 1997, Selective maintenance of a recombinant gene in a population of vaccine cells; Roy Curtiss, III, 424/93.2; 435/69.1, 71.2, 172.3, 252.3 [IMAGE AVAILABLE]

3. 5,595,889, Jan. 21, 1997, Process for integration of a chosen gene on the chromosome of a bacterium using Mu transposons; Fran.cedilla.ois Richaud, et al., 435/71.2, 69.1, 71.1, 172.3, 243, 252.3, 847, 849; 935/42, 52, 72, 73 [IMAGE AVAILABLE]

4. 5,387,744, Feb. 7, 1995, Avirulent microbes and uses therefor: Salmonella typhi; Roy Curtiss, III, et al., 424/235.1, 258.1; 435/172.3, 252.3, 252.33, 320.1, 879; 935/60, 62, 72 [IMAGE AVAILABLE]

=> d 2 ab

US PAT NO: 5,672,345 [IMAGE AVAILABLE] L7: 2 of 5

ABSTRACT:
The invention encompasses methods of maintaining desired recombinant genes in a genetic population of cells expressing the recombinant gene. The methods utilize mutant cells which are characterized by a lack of a functioning native gene encoding an enzyme which is essential for cell survival, wherein this enzyme catalyzes a step in the biosynthesis of an essential cell wall structural component and the presence of a first recombinant gene encoding an enzyme which is a functional replacement for the native enzyme, wherein the first recombinant gene cannot replace the defective chromosomal gene. The first recombinant gene is structurally linked to a second recombinant gene encoding a desired product. Loss of the first recombinant gene causes the cells to lyse when the cells are in an environment where a product due to the expression of the first recombinant gene is absent. The invention also encompasses methods of creating and isolating mutant cells with the above characteristics. The cells of the invention are useful for commercial production of desired products, for components of vaccines for immunizing individuals, and for release into the environment.

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